Editorials

Physicians as Role Models in Society

ROLE MODELS INFLUENCE people of all ages. As we grew up most of us were influenced by role models. Sometimes they were our parents, sometimes our teachers, sometimes athletes. Always, they were persons we admired or who stood for something we admired. Many of us, perhaps more than we remember or realize, have modeled ourselves and our behavior on our role models. As adults, we tend to conform to role models who share our daily lives.

There is something biological about role models. Animals learn how to get food and protect themselves from predators from role models, usually one or both of their parents. Humans have many more role models from which to select, and who these are and what they stand for profoundly affect many of us. Role models for youth may be found in the home, in the schools, on the streets, at the movies, or on television. Traditional role models are undermined when drugs, promiscuous sexual activity, and violence seem to permeate society and cheating and dishonesty are found in respected places. Role models do a great deal to shape society and that for which it stands.

There is much that could be said about role models in the medical profession. Many physicians are fine role models for their colleagues, their patients, and the communities in which they live. To the extent that there is greed, lust for power or prestige, or deviation from personal or ethical standards, the model may become tarnished. And there are many who believe that academic role models in medical schools perform something of a disservice by attracting students into subspecialties of bioscience and technology at the expense of weakening their interest in patients and patient care. But, by and large, physicians stand tall and steadfast and are respected for their personal discipline, their work ethic, and their dedication to patients and health care. They are standing up as best they can to the forces that beset them, and there is mounting evidence that, in any case, they are not about to desert their advocacy of the best care for their patients.

Today's society needs good role models. It may even need physicians as role models, not only for young physicians but for society as a whole. Health now touches almost every facet of society, and physicians have many points of contact with the public. At almost any of these points physicians can be teachers and role models. When physicians finally stopped smoking and took a firm stand, the tide was turned in the war against cigarette smoking. Physicians as role models did help to make a difference.

The medical profession is under stress, to be sure. But when successful under stress, role models, like anyone else, are often most influential and effective. All that is necessary is for physicians to live the reasons for which most entered the profession in the first place—a fascination with bioscience, a desire to help fellow humans needing their professional help, and a wish to use their lives in service to humanity. Living these reasons, which after all is doctoring, and combining this with teaching, which after all is also part of doctoring, can make physicians the very much needed role models in today's very health oriented society.

MSMW

Chronic Urticaria—A Frustrating but Increasingly Understandable Disorder

URTICARIA AND ITS RELATED SYNDROME, angioedema, are extraordinarily common disorders in medical practice, occurring in perhaps as many as 20% of the population at some time during their life. These disorders are also persistent, with many patients having repeated episodes for decades. The lesions are bothersome and mysterious to patients and are frustrating to clinicians. The very ease of their recognition, combined with the difficulty in defining an etiologic diagnosis, has led over the years to a variety of misapprehensions about this disease. Several important caveats need also to be added to any discussion of urticaria. As urticaria is a common disorder, it is not at all unusual for other findings to be noted in patients presenting with it. The conjunction of a common illness with an intercurrent problem does not imply cause and effect. Hence, numerous case reports indicating infection with parasites, occult dental or sinus infection, or other seemingly bizarre or biologically inexplicable associations may be merely the coincident occurrence of two unrelated events. This must always be kept in mind when explanations for urticaria are presented. For example, in one large review, causes of urticaria are listed that most would feel are unproved.[1] Nonetheless, urticaria is so common and is engendered by so many different events that it continues to provide an intellectual and diagnostic challenge to the most astute and persistent clinician. In this issue, Burrall and colleagues provide an up-to-date review of our current clinical understanding of urticaria and its treatment and emphasize our inadequate grasp of the pathobiology of this important syndrome.

Because of the role of histamine in inducing urticaria and the knowledge that histamine is present in the skin almost exclusively in mast cells, it has long been known that mast cells are central to understanding urticaria. Beginning in the early 1970s, it became apparent that various model systems could be used to manipulate cutaneous mast cells and thus tease apart the pathobiology of urticaria. Useful in this regard was, and has been, the model of idiopathic cold urticaria, a disorder that comprises approximately 1% to 2% of cases of chronic urticaria. In patients with this disorder whealing develops on exposure to cold, generally on rewarming of the affected part. This disease may be life-threatening in patients in whom after extensive exposure to cold, such as in bathing or boating accidents, extensive urticaria and angioedema develop, inducing hypotension, which can lead to death by drowning. The ability to activate cold urticaria in the laboratory produced the first model that allowed the obtaining of blood concurrent with lesion development, thereby enabling an analysis of possible molecular causes of urticaria. Histamine, chemoattractant molecules for neutrophils and eosinophils, and platelet-activating factor all have been identified within minutes of the application of cold.[2] In addition, biopsy specimens of the cold-challenged areas reveal mast cell degranulation. As this disorder in a large number of patients can be passively transferred with immunoglobulin (Ig) E antibody, this model system can be linked to that of allergic urticaria. Mast cell activation through IgE antibody and an-

tigen has long been recognized as a cause of acute urticaria, and, in those patients who are unable to avoid the antigen, of chronic urticaria. Rather than pollen antigens, which so commonly cause rhinitis, conjunctivitis, and asthma, the antigens that appear to be most common in the induction of chronic urticaria are foods and other ingestants, such as antibiotics. While food allergy is a highly controversial area and is much more commonly blamed than truly implicated, it is clear that in many patients, ingesting foods is associated with the development of urticaria. Using skin window techniques, it has been found that a variety of mediators are released into the skin on mast cell challenge with antigen in allergic patients.[3] Thus histamine, tryptase, prostaglandin D_2, leukotriene C_4, and platelet-activating factor all can be identified. The similarity of mediators generated by cold and by antigen further solidifies the link between the known IgE mast cell pathophysiology of allergic reactions with that of physical allergy. The potency of the vasoactive mediators generated by mast cells—histamine, leukotriene C_4, prostaglandin D_2, platelet-activating factor, and adenosine—provides a pathophysiologic substrate for inducing urticaria.

More recent developments in mast cell biology and tissue inflammation suggest important mechanisms in addition to IgE-mediated processes whereby mast cell activation may take place and thus urticaria engendered. It has long been recognized that biopsy specimens of urticarial lesions commonly contain infiltrating leukocytes, most particularly mononuclear leukocytes and lymphocytes. Recent work has also shown the dermal deposition of eosinophilic major basic protein at sites of urticaria, suggesting the previous presence of eosinophils and their activation during the development of urticaria (reviewed by Gleich and Adolphson).[4] Infiltrating eosinophils and mononuclear leukocytes can not only generate potent vasoactive mediators (leukotriene C_4, platelet-activating factor) but also release products capable of activating mast cells. Such activators include the eosinophilic major basic protein, neurotoxin, cationic peptide, and peroxidase,[4] and the monocyte products interleukin-1[5] and granulocyte-macrophage colony-stimulating factor.[6] In addition, a large family of molecules termed histamine-releasing factors are generated by monocytes, lymphocytes, and neutrophils.[7] These molecules are capable of activating mast cells and thus causing the release of biologically relevant mast cell mediators. Therefore, mast cell products can be made available to the local microenvironment of the skin and lead to urtication through direct allergen-IgE interactions, through the manipulation of IgE molecules on the surface of the cells through physical means (as in cold urticaria), and also by the participation of a variety of lymphokines, cytokines, and inflammatory cell constituents. This complex situation is further complicated by the knowledge that a number of neuropeptides,[8] including substance P, calcitonin gene-related peptide, vasoactive intestinal polypeptide, and adenosine triphosphate, all of which are present in fine nerve endings, have been shown to be potent degranulators of human cutaneous mast cells. Thus, a variety of signals can lead to urticaria through a similar final common pathway: the mast cell.

Recent advances in mast cell biology have identified two subpopulations of this cell in humans—a mucosal type prominent in gut and peripheral airway, which is dependent on T-lymphocyte growth factors (interleukin-3 and -4),[9] and a connective tissue type found prominently in skin[10] and on serosal surfaces and not directly T-lymphokine regulated. Although all mast cells respond to IgE-mediated signals, the cutaneous mast cell differs from the mucosal type in being extremely sensitive to activation by neuropeptides, but these do not affect the mucosal mast cells. This difference likely underlies the fact that urticaria is so common, appears to be induced by such disparate triggers, and often occurs in the absence of other symptoms felt due to mast cells and their mediators—that is, rhinitis, asthma, conjunctivitis.

The new understanding of mast cell activation has yet to be exploited therapeutically, but recent major advancements have been made in the treatment of urticaria and angioedema. These include the development of new, potent compounds for the treatment of these disorders, particularly new nonsedative antihistaminic compounds. These agents, discussed in the review by Burrall and co-workers, share an inability to cross the blood-brain barrier and, hence, do not interfere with cognition and alertness, while still potently blocking the H_1 receptor. Such drugs have quickly become the mainstay of therapy in urticaria. These new agents have also been supplemented by the discovery that tricyclic antidepressants are extremely potent (if sedating) antihistamines. One of these, doxepin hydrochloride, has also assumed an important place in the treatment of severe, recalcitrant urticaria. It is exciting, however, to contemplate the new pharmacopeia for urticaria as the therapeutic possibilities made available by our new knowledge of mast cell activators are explored.

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Biological Significance of *Giardia*-Specific Antibodies

THE PAST DECADE has been a time of substantial growth in the understanding of immunologic responses against *Giardia lamblia*. The realization that such responses contribute to the clearance of *Giardia* infection came originally from the finding that hypogammaglobulinemia predisposes to chronic giardiasis. Subsequent clinical and experimental studies have generated a relatively coherent picture of *Giardia*-specific